

REMARKS

Claims 1-15 were pending in the present application. Claims 13-15 were rejected. Claims 4-6 and 11 are herein cancelled without prejudice. Claims 13-15 are herein amended. New claims 16-20 are herein added. No new matter has been added.

Information Disclosure Statement

The Office Action objected to the Information Disclosure Statement filed on November 29, 2006 by striking through Tanaka et al. ("GTP-Binding Proteins," Experimental Medical Science, vol. 21, No. 2 (2003), p. 19-26") and indicating that it is not in English. However, Applicants respectfully clarify that this reference is cited in the specification at paragraph [0002]. Applicants herein amend the specification and provide a supplemental IDS, so that that the citation in the specification matches the citation on the IDS. Applicants note that the Tanaka lists two sets of page numbers: pages 19-26 from the "extra" numbering sequence, and pages 137-145 from the "sequential" numbering sequence. Applicants further submit that the English discussion of Tanaka in paragraph [0002] is sufficient to satisfy the requirement for a concise statement of relevance as required in MPEP 609.04(a). As such, Applicants respectfully request that the Examiner initial the supplemental IDS to indicate that Tanaka has been considered. Other documents are also submitted in this supplemental IDS from the supplementary European Search Report.

Furthermore, Applicants noted that the last line of paragraph [0009] refers to "J. Atheroscler. Thromb., 11:62-183, 2004." However, this is an error. As such, Applicants herein amend the specification to correct this citation such that the page numbers are 62-72.

Finally, Applicants note that the Office Action lined through the International Search Report and the International Preliminary Report on Patentability, and noted "no pub data." Applicants respectfully note that these documents are dated June 7, 2005 and September 28, 2006, and are provided merely for their potential materiality to patentability. Applicants respectfully request that the Examiner initial these documents as being considered.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 13-15 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action asserts that the meaning of "a blood vessel remedy" is unclear from the claim and the specification. Thus, the Office Action states that one having ordinary skill in the art would not be able to ascertain the metes and bounds of the claims. In response, Applicants herein amend the claims to recite a method of screening for "a substance which improves endothelial functions." Applicants respectfully submit that this amendment is supported at least by paragraph [0008]. Additionally, Applicants herein make other amendments to claims 13-15 in order to improve their clarity and form. Favorable reconsideration is respectfully requested.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 13-15 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Office Action asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is noted that the enablement rejection is based on the presumption that "blood vessel remedy" means "a substance that is capable of treating a vascular disease or condition such as atherosclerosis."

The Office Action identifies five main issues:

1. Whether the method can be applied to any test substance.
2. Whether the method can be applied to any vascular disease or condition.
3. The amount of Rac that must be transferred into the nucleus in order for a test compound to be considered a remedy is not explained.
4. The period of time in which Rac is allowed to transfer into the nucleus is not explained.
5. It is not demonstrated that translocation of Rac into the nucleus is responsible for pitavastatin's therapeutic effects.

With respect to the first issue, Applicants respectfully submit that the fact that the claimed method can be applied to any "test substance" does not render the claims not enabled. Rather, the fact that any test substance can be screened is precisely the "point" of a screening assay. Furthermore, the cell is further specified as a HUVEC. Additionally, the protein which is observed for possible transfer is further specified to be a labelled Rac protein.

As to the second issue, Applicants first note that the claims are amended to recite screening for a substance “which improves endothelial function.” Applicants respectfully note that paragraph [0008] of the specification discusses the known functions of Rac protein generally, while paragraph [0020] recites the correlation between the pharmaceutical composition and the nucleus transfer. Additionally, Masamura et al., which was cited in the ISR (*K. Masamura, et al., Arterioscler. Thromb. Vasc. Biol. 2003, 23, 512-517*), discloses the behavior of pitavastatin in HUVEC, which is also used in Example 1 of the instant specification. Masamura et al. discloses that pitavastatin has an ability to induce thrombomodulin (TM) expression, thus improving endothelial functions. Figure 5 on page 515 shows the significantly enhanced TM expression by *Clostridium sordellii* lethal toxin (LT), which is an inhibitor of Rac protein. Figure 1 on page 513 shows that the Rac protein is responsible for the behavior of pitavastatin. Accordingly, it is demonstrated that the inhibition of Rac activity results in the improvement of endothelial functions. As shown in Fig. 1 of the specification, the distribution of the Rac protein in the entire area of the HUVEC is commonly observed. However, as shown in Figs. 2 and 3, the addition of pitavastatin promotes the transfer of the Rac protein into a nucleus. Accordingly, the Rac protein loses its activity within the cell, resulting in the improvement of endothelial functions (see Masamura *et al.*). This means that if the transfer of the labeled Rac protein into the nucleus has been visually identified in response to the addition of the test substance to the HUVEC, it is confirmed that the test substance which was screened is identified as a substance which improves endothelial functions.

As to the third issue, Applicants note that the claims are herein amended to recite that the Rac protein a “labeled Rac protein.” Paragraph [0023] of the specification explains that “[t]he method is particularly preferably a method which involves preparing a fusion protein of a fluorescence protein such as GFP and Rac protein and then visually identifying the transfer of the fusion protein into the nucleus.” Accordingly, the visual identification is satisfactory to determine whether transfer of the Rac protein into the nucleus has occurred. If the transfer of Rac protein into nucleus has visually been identified, the test substance is thus proved to be a substance which improves endothelial functions. As such, Applicants respectfully submit that the amount of Rac that must be transferred into the nucleus in order for the test substance to be considered “a substance which improves endothelial functions” is sufficiently explained.

As to the fourth issue, Applicants respectfully submit that the period of time over which the HUVEC should be monitored for Rac transfer depends on the culture condition of the HUVEC. This can be suitably determined by one having ordinary skill in the art. The monitoring time period can readily be determined by one having ordinary skill in the art also by reference to the condition shown in Example 1 of the instant specification, in which the time period is 15 hours. Additionally, Masamura et al. sets the time period to 24 hours for treatment of HUVEC in accordance with the common knowledge in the art (See page 513, right column, last two lines). In view of the above, Applicants respectfully submit that the approximate stimulus-response time in HUVEC is well known among those skilled in the art. As such, the time period for the claimed embodiments could have readily been determined in accordance with the common knowledge in the art, without requiring undue experimentation. Furthermore,

Applicants herein add claim 15, which recites that measurement is done 15 hours after the test substance is added.

As to the fifth issue, Applicants respectfully reiterate that this sufficiently demonstrated in the art, as discussed above with respect to the second issue. In view of documents such as Masamura *et al.*, Applicants respectfully submit that one having ordinary skill in the art would understand that the transfer of the Rac protein into the nucleus is responsible for pitavastatin's therapeutic effects.

In view of the above, Applicants respectfully submit that it is clearly disclosed in the specification that the test substance (*i.e.* the substance tested for the effect on endothelial functions) is added to the culture of HUVEC expressing the labeled Rac protein; followed by the HUVEC being stimulated and subjected to culture for the time period of response (*i.e.* for the time period commonly known in the art), during which the labeled Rac protein is visually identified. Accordingly, Applicants respectfully submit that one having ordinary skill in the art could make and use the recited embodiments without undue experimentation. As such, Applicants respectfully submit that the pending claims fully comply with the enablement requirement. Favorable reconsideration is respectfully requested.

New Claims

In addition to claims 13-16, as discussed above, Applicants herein add new claims 17-20. Instead of reciting a method of screening for a substance to improve endothelial functions, new claims 17-20 recite a method for screening for a substance *which promotes nuclear transfer of*

Rac protein. These new claims are supported by the specification in general, for example, paragraph [0031]. Examination of these claims is respectfully requested.

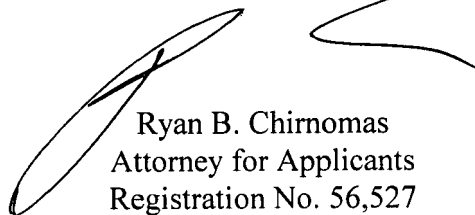
For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

If the Examiner deems that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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Enclosure: Supplemental IDS